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Nano-Scale non ionic surfactant vesicles for drug delivery

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KEYWORDS

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ABSTRACT:

Nano-scale non-ionic surfactant vesicles (NSVs) have emerged as promising candidates for targeted drug delivery. These vesicles, commonly referred to as liposomes, are small spherical structures composed of a lipid bilayer enclosing an aqueous compartment. The small size of liposomes allows them to cross biological barriers and target specific cells or tissues. The non-ionic nature of the surfactant used in the formulation prevents aggregation and allows for stability in various physiological environments. These vesicles can be customized by varying the lipid composition and surface modifications, modulating the drug release profile and stability, and enhancing therapeutic efficacy. NSVs offer advantages such as high drug loading capacity, controlled release kinetics, and tunable surface properties, making them attractive candidates for drug delivery. In vivo studies have demonstrated the efficacy of NSVs in various disease models, including cancer, infectious diseases, inflammatory disorders, and neurological conditions. Clinical trials have further evaluated NSVs for drug delivery applications, focusing on safety, efficacy, and pharmacokinetics in human subjects. Challenges in clinical translation, such as ensuring safety, optimizing pharmacokinetics, and obtaining regulatory approval, remain, but ongoing research efforts continue to advance NSV-based drug delivery technologies. Collaborative efforts between researchers, clinicians, industry partners, and regulatory agencies are crucial for realizing the full potential of NSVs as safe, effective, and clinically viable drug delivery systems for addressing unmet medical needs and enhancing healthcare delivery worldwide.

Introduction

In the realm of pharmaceuticals, drug delivery systems play a crucial role in enhancing therapeutic efficacy, minimizing side effects, and improving patient compliance[1]. These systems are designed to efficiently transport drugs to their target sites within the body while minimizing systemic exposure. Among the diverse array of drug delivery systems, nano-scale non-ionic surfactant vesicles (NSVs) have emerged as promising candidates due to their unique properties and versatile applications[2]. This introduction aims to provide a comprehensive overview of drug delivery systems, introduce NSVs, and highlight their significance and potential advantages in drug delivery. Drug delivery systems encompass a wide range of technologies and formulations aimed at optimizing the delivery of therapeutic agents to target tissues or cells within the body. Traditional drug delivery methods, such as oral tablets and injections, often suffer from limitations such as poor bioavailability, rapid clearance, and off-target effects[3]. To address these challenges, researchers have developed various sophisticated drug delivery systems that offer targeted delivery, controlled release, and enhanced efficacy. One prominent category of drug delivery systems is nanoparticulate carriers, which are engineered to deliver drugs at the nano-scale level. These carriers include liposomes, polymeric nanoparticles, dendrimers, and

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micelles, among others[4]. They offer several advantages, including increased drug solubility, prolonged circulation time, and targeted delivery to specific tissues or cells. Nano-scale non-ionic surfactant vesicles, or NSVs, are nano-sized vesicular structures composed of amphiphilic non-ionic surfactants[5]. These surfactants possess both hydrophilic and hydrophobic moieties, allowing them to self-assemble into bilayered vesicles in aqueous environments. NSVs typically range in size from 10 to 100 nanometers and can encapsulate hydrophilic, hydrophobic, or amphiphilic drugs within their aqueous core or lipid bilayers. NSVs offer several advantages as drug delivery carriers, including high drug loading capacity, stability in biological fluids, and tunable surface properties for targeting specific tissues or cells. Their nano-scale size allows for efficient penetration into biological barriers and accumulation at target sites, thereby enhancing therapeutic efficacy while minimizing systemic toxicity[6]. The unique properties of NSVs make them promising candidates for various drug delivery applications. One of the key advantages of NSVs is their ability to encapsulate a wide range of therapeutic agents, including small molecules, proteins, nucleic acids, and imaging agents[3]. This versatility enables the delivery of diverse classes of drugs with different physicochemical properties, expanding the scope of potential applications in cancer therapy, infectious diseases, and regenerative medicine. Furthermore, NSVs offer precise control over drug release kinetics, allowing for sustained release or triggered release in response to specific stimuli such as pH, temperature, or enzymatic activity[5]. This controlled release profile can improve drug efficacy, reduce dosing frequency, and minimize side effects compared to conventional drug delivery formulations. Another important advantage of NSVs is their biocompatibility and biodegradability, which are essential for safe and effective drug delivery[7]. NSVs composed of biocompatible surfactants such as phospholipids or block copolymers are well-tolerated by the body and exhibit minimal immunogenicity or toxicity. Additionally, the biodegradable nature of NSVs ensures the clearance of carrier materials from the body after drug release, reducing the risk of long-term accumulation or adverse effects.

Structure and Properties of NSVs

A. Composition and Structure of NSVs:

Nano-scale non-ionic surfactant vesicles (NSVs) are nano-sized vesicular structures composed of amphiphilic non-ionic surfactants[66]. These surfactants consist of a hydrophilic head group and a hydrophobic tail group. When dispersed in an aqueous solution, the surfactant molecules self-assemble into bilayered vesicles due to the hydrophobic interactions between the tail groups and the hydrophilic interactions between the head groups and water molecules. The composition of NSVs can vary depending on the choice of surfactant and other additives[3]. Commonly used surfactants for NSV preparation include non-ionic surfactants such as phospholipids, block copolymers, and fatty acids. Phospholipids, such as phosphatidylcholine and phosphatidylglycerol, are widely employed due to their biocompatibility and ability to form stable vesicles. Block copolymers, such as poloxamers and poloxamines, offer versatility in tailoring the physicochemical properties of NSVs[8]. The structure of NSVs is characterized by a spherical or ellipsoidal shape with a lipid bilayer membrane enclosing an aqueous core. The bilayer membrane consists of two layers of surfactant molecules arranged with their hydrophobic tails facing inward and their hydrophilic heads facing outward towards the aqueous environment[34]. This bilayer structure provides a barrier that encapsulates drugs within the aqueous core or lipid bilayers, protecting them from degradation and facilitating controlled release.

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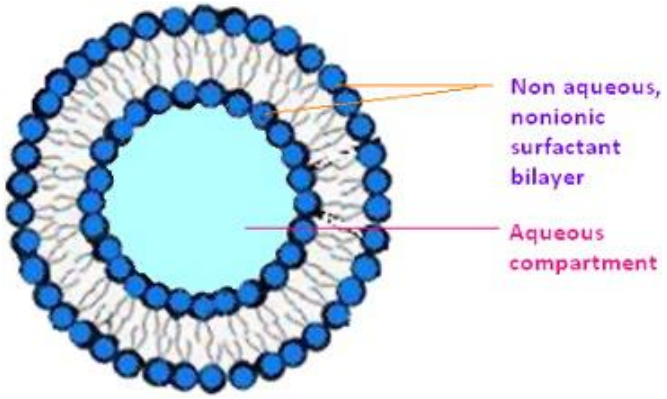

Figure 1: Structure of non ionic surfactant.

B. Physical and Chemical Properties Influencing Drug Delivery:

The physical and chemical properties of NSVs play a critical role in determining their behavior and performance as drug delivery carriers. These properties can be tailored through careful selection of surfactants, additives, and preparation methods to achieve desired drug delivery outcomes[9].

1. Size and Size Distribution: The size of NSVs is a crucial parameter that influences their biodistribution, cellular uptake, and drug release kinetics. NSVs typically range in size from 10 to 100 nanometers, allowing them to penetrate biological barriers and accumulate at target sites. Control over size distribution is essential to ensure uniform drug delivery and minimize variability in therapeutic efficacy.

2. Surface Charge: The surface charge of NSVs, determined by the composition of surfactants and additives, influences their interaction with biological membranes and cells[6]. Positively charged NSVs (cationic) tend to exhibit enhanced cellular uptake via electrostatic interactions with negatively charged cell membranes, making them suitable for targeted drug delivery to specific cell types. Conversely, negatively charged NSVs (anionic) may have prolonged circulation times due to reduced uptake by reticuloendothelial system (RES) cells[10].

3. Stability: The stability of NSVs in biological fluids is crucial for maintaining drug encapsulation and preventing premature drug release. Factors such as surfactant composition, lipid packing density, and presence of stabilizing agents influence NSV stability against aggregation, fusion, and degradation. Stable NSVs exhibit prolonged circulation times in vivo and enhanced drug delivery efficiency[64].

4. Drug Loading Capacity: The ability of NSVs to encapsulate drugs within their aqueous core or lipid bilayers depends on factors such as drug solubility, partition coefficient, and interaction with surfactant molecules. NSVs offer high drug loading capacities for both hydrophilic and hydrophobic drugs, allowing for efficient delivery of a wide range of therapeutic agents[11].

5. Drug Release Kinetics: The release kinetics of drugs from NSVs can be modulated by altering the properties of the vesicle membrane, such as lipid composition, bilayer fluidity, and presence of pore-forming agents. Controlled release formulations can be designed to achieve sustained release, triggered release in response to specific stimuli, or rapid release for immediate therapeutic effect[12].

C. Comparison with Other Drug Delivery Systems:

NSVs offer several advantages over other drug delivery systems, making them attractive candidates for various biomedical applications.

1. Liposomes: Liposomes are lipid-based vesicular structures similar to NSVs but typically larger in size and

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composed of phospholipids. While both liposomes and NSVs exhibit biocompatibility and high drug loading capacities, NSVs offer greater stability, tunable surface properties, and enhanced penetration into biological barriers due to their smaller size and simpler composition[13].

2. Polymeric Nanoparticles: Polymeric nanoparticles are synthetic particles composed of biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) or polyethylene glycol (PEG). While polymeric nanoparticles offer tunable drug release kinetics and surface modifications for targeted delivery, they may exhibit batch-to-batch variability and require complex synthesis methods. NSVs, on the other hand, offer a simpler preparation process and greater versatility in drug encapsulation[9].

3. Micelles: Micelles are colloidal assemblies of amphiphilic molecules that form spherical or rod-like structures in aqueous solutions. While micelles offer high drug loading capacities and improved solubility for hydrophobic drugs, they may suffer from limited stability and rapid drug release kinetics. NSVs provide greater stability and control over drug release, making them suitable for sustained delivery of therapeutic agents[14].

Methods of Preparation

A. Various Techniques for NSV Synthesis:

Nano-scale non-ionic surfactant vesicles (NSVs) can be prepared using a variety of techniques, each offering unique advantages in terms of scalability, versatility, and control over vesicle properties. Some of the commonly used methods for NSV synthesis include:

1. Thin Film Hydration Method: This method involves dissolving the surfactant and any additives in an organic solvent to form a thin lipid film on the walls of a round-bottom flask or glass vial[7]. The solvent is then evaporated under reduced pressure or nitrogen gas to form a dry lipid film, which is subsequently hydrated with an aqueous solution containing the drug of interest. The hydration process leads to the formation of NSVs, which can be further processed by sonication or extrusion to achieve desired size and homogeneity[15].

2. Reverse Phase Evaporation Method: In this method, an organic phase containing the surfactant and lipid components is emulsified with an aqueous phase containing the drug using high-shear mixing or homogenization. The organic solvent is then evaporated under reduced pressure or by gentle heating, leading to the formation of NSVs in the aqueous phase. This method is particularly suitable for encapsulating hydrophobic drugs within the lipid bilayers of NSVs[6].

3. Solvent Injection Method: In this technique, the surfactant and lipid components are dissolved in an organic solvent, and the resulting solution is rapidly injected into an aqueous phase under high shear or sonication[6]. The rapid mixing of the organic and aqueous phases leads to the spontaneous formation of NSVs due to the self-assembly of surfactant molecules at the interface between the two phases. This method offers simplicity and scalability for large-scale production of NSVs[16].

4. Microfluidic-Based Method: Microfluidic devices utilize microscale channels and precise control over fluid flow to generate highly uniform droplets or vesicles with controlled size and composition. In microfluidic-based NSV synthesis, the surfactant and lipid components are introduced into separate inlet channels, and their controlled mixing at a junction leads to the formation of NSVs. This method offers excellent control over vesicle size and composition and is suitable for high-throughput screening of formulation parameters[17].

B. Factors Affecting the Preparation Process:

Several factors influence the efficiency and characteristics of NSV preparation, including the choice of surfactants, lipid components, additives, and processing conditions. Some key factors to consider include:

1. Surfactant and Lipid Composition: The selection of surfactants and lipids plays a crucial role in determining the stability, size, and drug loading capacity of NSVs. Surfactants with appropriate hydrophilic-lipophilic balance (HLB) and lipid components with high purity and biocompatibility are essential for successful NSV formation[18].

2. Drug Compatibility: The physicochemical properties of

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the drug, including solubility, partition coefficient, and stability, influence its encapsulation efficiency and release kinetics within NSVs. Hydrophobic drugs may preferentially partition into the lipid bilayers of NSVs, while hydrophilic drugs may be encapsulated within the aqueous core[7].

3. Processing Conditions: Parameters such as temperature, pH, and mixing intensity during NSV preparation can affect vesicle size, homogeneity, and stability. Optimization of processing conditions is necessary to achieve reproducible and uniform NSV formulations[19].

4. Additives and Stabilizers: Incorporation of stabilizing agents, such as cholesterol, polyethylene glycol (PEG), or antioxidants, can enhance the stability and shelf-life of NSVs by preventing aggregation, fusion, or oxidative degradation. Additionally, functional additives such as targeting ligands or stimuli-responsive moieties can be incorporated to impart specific functionalities to NSVs for targeted drug delivery[20].

C. Optimization Strategies for Enhanced Drug Encapsulation Efficiency:

Achieving high drug encapsulation efficiency is essential for maximizing the therapeutic efficacy of NSVs and minimizing wastage of costly drug substances. Several strategies can be employed to optimize drug encapsulation within NSVs:

1. Pre-formulation Studies: Comprehensive characterization of drug physicochemical properties, including solubility, partition coefficient, and stability, is essential for selecting appropriate formulation components and optimizing formulation parameters[21].

2. Selection of Surfactants and Lipids: Screening of surfactants and lipids with different physicochemical properties can help identify formulations that offer optimal drug encapsulation efficiency. Surfactants with high self-assembly propensity and lipid components with suitable bilayer packing properties are preferred for efficient drug loading[22].

3. Formulation Optimization: Systematic optimization of formulation parameters such as surfactant-to-lipid ratio, drug-to-lipid ratio, and hydration conditions can help maximize drug encapsulation efficiency while maintaining vesicle stability and size uniformity[5].

4. Co-solvent or Co-surfactant Addition: Addition of co-solvents or co-surfactants with high drug solubility can enhance drug loading efficiency by promoting drug partitioning into NSVs during the hydration process. However, care must be taken to ensure compatibility with the final formulation and minimize potential toxicity or destabilization effects[23].

5. Post-formulation Processing: Post-formulation techniques such as sonication, extrusion, or freeze-thaw cycling can be employed to further optimize drug encapsulation efficiency and vesicle size distribution. These methods help disrupt large vesicles or aggregates and promote drug diffusion into NSVs, leading to improved drug loading[24].

Drug Loading and Release Mechanisms

Drug loading and release mechanisms are crucial aspects of nano-scale non-ionic surfactant vesicles (NSVs) as drug delivery systems. Understanding how drugs are encapsulated within NSVs and how they are released from these vesicles is essential for optimizing drug delivery efficiency and therapeutic efficacy[25].

A. Mechanisms of Drug Encapsulation within NSVs:

The encapsulation of drugs within NSVs can occur through various mechanisms, depending on the physicochemical properties of the drug and the structure of the vesicles. Some common mechanisms of drug encapsulation within NSVs include:

1. Partitioning into Lipid Bilayers: Hydrophobic drugs can partition into the lipid bilayers of NSVs, where they are solubilized within the hydrophobic core of the bilayer. This mechanism is favored for drugs with high lipid solubility and low aqueous solubility, allowing them to be efficiently encapsulated within NSVs[26].

2. Encapsulation within Aqueous Core: Hydrophilic drugs can be encapsulated within the aqueous core of NSVs, where they are solubilized in the aqueous phase surrounded by the lipid bilayer membrane. This mechanism is suitable for drugs with high aqueous solubility and low lipid

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solubility, allowing them to be stably incorporated within NSVs[27].

3. Complexation with Surfactants: Some drugs can form complexes with the surfactant molecules present in NSVs, leading to their encapsulation within the vesicle structure. This mechanism is particularly relevant for drugs that exhibit affinity for specific surfactants or undergo complexation-driven encapsulation[19].

4. Entrapment during Vesicle Formation: During the formation of NSVs, drugs may become entrapped within the vesicle structure due to physical entrapment or entrapment during the hydration process. This mechanism can contribute to drug encapsulation within NSVs, especially for drugs with suitable physicochemical properties[28].

B. Factors Influencing Drug Loading Efficiency:

Several factors influence the drug loading efficiency of NSVs, including the physicochemical properties of the drug, the composition of the vesicle formulation, and the preparation method used[29]. Understanding and optimizing these factors are essential for achieving high drug loading efficiency and maximizing therapeutic efficacy. Some key factors influencing drug loading efficiency in NSVs include:

1. Drug Properties: The physicochemical properties of the drug, including solubility, partition coefficient, and molecular weight, play a critical role in determining its encapsulation efficiency within NSVs. Drugs with high lipid solubility and low aqueous solubility are more likely to be efficiently encapsulated within the lipid bilayers of NSVs, while hydrophilic drugs may preferentially partition into the aqueous core[30].

2. Surfactant and Lipid Composition: The choice of surfactants and lipids used in NSV formulation significantly impacts drug loading efficiency. Surfactants with suitable hydrophilic-lipophilic balance (HLB) and lipid components with high lipid solubility and biocompatibility are preferred for efficient drug encapsulation. Optimization of the surfactant-to-lipid ratio and the addition of co-surfactants or co-solvents can also enhance drug loading efficiency[31].

3. Formulation Parameters: Various formulation parameters, such as the drug-to-lipid ratio, hydration conditions, and processing methods, influence drug loading efficiency in NSVs. Optimization of these parameters is essential to achieve maximum drug encapsulation while maintaining vesicle stability and size uniformity[32].

4. Drug-Lipid Interactions: Interactions between the drug molecules and the lipid bilayers of NSVs can significantly affect drug loading efficiency. Hydrophobic drugs may partition into the lipid bilayers, while hydrophilic drugs may interact with the aqueous core or the lipid head groups. Understanding these interactions is critical for optimizing drug loading efficiency in NSVs[33].

C. Release Kinetics and Mechanisms of Drug Release from NSVs:

The release kinetics and mechanisms of drug release from NSVs play a crucial role in determining the therapeutic efficacy and duration of drug action[34]. Various factors, including vesicle properties, drug properties, and environmental conditions, influence drug release kinetics from NSVs. Some common mechanisms of drug release from NSVs include:

1. Diffusion-Controlled Release: In diffusion-controlled release, drug molecules diffuse through the lipid bilayers or aqueous channels of NSVs, driven by concentration gradients. This mechanism is predominant for drugs encapsulated within the lipid bilayers or dispersed in the aqueous core of NSVs. The rate of drug release is influenced by factors such as drug solubility, lipid membrane permeability, and vesicle size[34].

2. Erosion or Disintegration: In erosion or disintegration-controlled release, NSVs degrade or disintegrate over time, leading to the release of encapsulated drug molecules. This mechanism may occur due to hydrolysis of lipid components, enzymatic degradation, or physical destabilization of the vesicle structure[41]. The rate of drug release is influenced by factors such as vesicle stability, lipid composition, and environmental conditions[35].

3. Stimuli-Responsive Release: Stimuli-responsive NSVs are designed to release drug molecules in response to

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specific stimuli such as pH, temperature, light, or enzymatic activity. These NSVs may incorporate stimuli-responsive moieties or undergo structural changes in response to external stimuli, leading to triggered drug release. This mechanism enables spatiotemporal control over drug release and can be utilized for targeted drug delivery and site-specific therapy[36].

4. Burst Release: In some cases, NSVs may exhibit burst release, where a significant portion of encapsulated drug molecules is rapidly released from the vesicles upon administration. Burst release may occur due to incomplete encapsulation, surface-associated drug molecules, or structural defects in the vesicle membrane. Minimizing burst release and achieving sustained release profiles are essential for optimizing the therapeutic efficacy and minimizing side effects of NSV-based drug delivery systems[37].

Applications in Drug Delivery

Nano-scale non-ionic surfactant vesicles (NSVs) have emerged as versatile drug delivery systems with numerous applications in medicine. Their unique properties, including high drug loading capacity, controlled release kinetics, and tunable surface properties, make them attractive candidates for targeted and controlled drug delivery[38].

A. Targeted Drug Delivery using NSVs:

Targeted drug delivery aims to deliver therapeutic agents specifically to diseased tissues or cells while minimizing systemic exposure and off-target effects[12]. NSVs offer several advantages for targeted drug delivery, including the ability to modify their surface properties with targeting ligands or antibodies for selective binding to specific receptors or biomarkers on target cells[39]. This allows for enhanced accumulation and uptake of NSVs at the site of action, leading to improved therapeutic efficacy and reduced side effects. One approach for targeted drug delivery using NSVs is to functionalize their surface with ligands that recognize overexpressed receptors on target cells[40]. For example, NSVs decorated with antibodies or peptides targeting tumor-specific antigens can selectively bind to cancer cells and deliver cytotoxic drugs or therapeutic payloads specifically to the tumor site. This targeted delivery approach minimizes systemic exposure to the drug, reducing toxicity to healthy tissues and improving patient outcomes. Moreover, NSVs can exploit the enhanced permeability and retention (EPR) effect, which is commonly observed in tumors due to their leaky vasculature and poor lymphatic drainage[41]. NSVs can passively accumulate in tumor tissues through the EPR effect, where they release therapeutic agents locally, further enhancing their efficacy against cancer cells while sparing normal tissues[29]. In addition to cancer therapy, targeted drug delivery using NSVs holds promise for various other applications, including treatment of inflammatory diseases, infectious diseases, and neurological disorders. By engineering NSVs with specific targeting moieties, researchers can tailor drug delivery systems to address the unique challenges associated with each disease, maximizing therapeutic benefits while minimizing adverse effects[42].

B. NSVs for Controlled Release of Therapeutic Agents:

Controlled release drug delivery systems allow for precise modulation of drug release kinetics, enabling sustained release over extended periods or triggered release in response to specific stimuli. NSVs offer excellent control over drug release kinetics, making them ideal candidates for developing controlled release formulations with enhanced therapeutic efficacy and patient compliance[43]. The controlled release of therapeutic agents from NSVs can be achieved through various mechanisms, including diffusion-controlled release, erosion or degradation-controlled release, and stimuli-responsive release[44]. By adjusting formulation parameters such as lipid composition, vesicle size, and surface modifications, researchers can tailor NSVs to exhibit specific release profiles suitable for different therapeutic applications[23]. For example, NSVs can be designed to release drugs gradually over time, maintaining therapeutic drug levels within the therapeutic window and minimizing fluctuations in plasma drug concentrations[45]. This sustained release profile is particularly beneficial for chronic conditions requiring long-term drug therapy, such as diabetes, hypertension, and pain management. Moreover, NSVs can be engineered to respond to external

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stimuli such as pH, temperature, or enzymatic activity, triggering controlled release of drugs at the desired site of action[46]. Stimuli-responsive NSVs undergo structural changes or drug release mechanisms in response to specific stimuli, enabling spatiotemporal control over drug delivery and minimizing off-target effects[44]. Controlled release formulations using NSVs have applications in various therapeutic areas, including cardiovascular diseases, infectious diseases, and neurodegenerative disorders[47]. By optimizing formulation parameters and understanding the underlying mechanisms of drug release, researchers can develop NSV-based controlled release systems with tailored release kinetics and improved therapeutic outcomes[48]. The application of niosomes in delivering drugs is summarized in Table 1 below.

Table 1: Summary of the Application of Niosomes in Drug Delivery

Surfactant	Formulation Method	Loaded Drug	Encapsulation Rate (%)	Administrated	Application	References
Span 60	Thin film hydration	Colchicine	90	Oral	Anti-inflammatory	[48]
Tween 80	Reverse-phase evaporation	Retinyl palmitate	Not specified	Topical	Skin care	[49]
Span 60/Tween 80	Reverse-phase evaporation	Acetazolamide	Not specified	Ophthalmic	Glaucoma treatment	[50]
Span 80/Tween 80	Thin film hydration	Zidovudine	Not specified	Oral	Antiretroviral therapy	[51]
Various nonionic surfactants	Not specified	Paclitaxel	Not specified	Oral	Cancer chemotherapy	[52]
Span 80/Tween 80	Not specified	Ketoconazole	Not specified	Topical	Antifungal treatment	[53]
Span 60/Tween 80	Not specified	Ketoprofen	Not specified	Topical	Anti-inflammatory	[54]
Various nonionic surfactants	Not specified	Terbinafine hydrochloride	Not specified	Topical	Antifungal treatment	[55]

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Various nonionic surfactants	Not specified	Lansoprazole	Not specified	Oral	Gastric acid suppression	[56]
Span 60/Tween 80	Not specified	Isoniazid	Not specified	Topical	Tuberculosis treatment	[57]

C. NSVs in Overcoming Biological Barriers for Drug Delivery:

Effective drug delivery often requires overcoming biological barriers such as the blood-brain barrier (BBB), gastrointestinal (GI) barrier, and skin barrier to achieve therapeutic concentrations of drugs at the target site[58]. NSVs offer unique advantages for traversing these barriers and delivering therapeutic agents to inaccessible or protected tissues. One of the most challenging barriers in drug delivery is the BBB, which limits the penetration of drugs into the central nervous system (CNS) and hinders the treatment of neurological disorders[54]. NSVs can be engineered to bypass or overcome the BBB through various strategies, including surface modifications with BBB-targeting ligands, such as peptides or antibodies, or utilizing endogenous transport mechanisms for efficient drug delivery to the brain. Similarly, NSVs can be designed to improve drug delivery across the GI barrier, enhancing oral bioavailability and therapeutic efficacy of orally administered drugs[59]. By incorporating mucoadhesive polymers or surface modifications that promote intestinal absorption, NSVs can enhance drug permeation through the intestinal mucosa and facilitate drug absorption into systemic circulation[33]. Moreover, NSVs hold promise for transdermal drug delivery, allowing for non-invasive administration of therapeutics through the skin. NSVs can penetrate the stratum corneum barrier and deliver drugs directly to underlying tissues or systemic circulation, bypassing first-pass metabolism and improving drug bioavailability[60].

Biocompatibility and Toxicity Assessment

Nano-scale non-ionic surfactant vesicles (NSVs) hold significant promise as drug delivery systems due to their unique properties and versatile applications. However, ensuring their biocompatibility and addressing potential toxicity concerns are essential steps in the development of safe and effective therapeutic formulations.

A. Evaluation of Biocompatibility of NSVs:

Biocompatibility refers to the ability of a material to perform its intended function without eliciting adverse effects on biological systems. Assessing the biocompatibility of NSVs involves evaluating their interactions with biological tissues, cells, and organs to ensure compatibility and minimize immune responses or inflammatory reactions[61].

1. In vitro Studies: In vitro studies are commonly used to assess the biocompatibility of NSVs with various cell types, including primary cells, cell lines, and co-culture systems. Cell viability assays, such as MTT or Alamar Blue assays, can be used to evaluate the cytotoxicity of NSVs and their effects on cell proliferation and viability. Additionally, assays measuring inflammatory cytokine release, cell morphology, and cellular uptake can provide valuable insights into the biocompatibility of NSVs[62].

2. In vivo Studies: In vivo studies are essential for evaluating the biocompatibility of NSVs in complex biological systems and assessing their biodistribution, pharmacokinetics, and tissue compatibility[4]. Animal models, such as mice, rats, or rabbits, can be used to investigate acute and chronic toxicity, immunogenicity, and tissue response to NSVs following systemic or local administration. Histological analysis of tissues, blood chemistry, and immune response markers can provide valuable information on the biocompatibility and safety profile of NSVs in vivo[63].

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3. Hemocompatibility: Hemocompatibility assessment evaluates the interaction of NSVs with blood components, including red blood cells, platelets, and plasma proteins, to ensure minimal hemolytic activity, thrombogenicity, and coagulation activation. Hemolysis assays, coagulation assays, and platelet aggregation studies can be performed to assess the hemocompatibility of NSVs and identify potential adverse effects on blood components[34].

B. Assessment of Potential Toxicity and Safety Concerns:

Despite their potential therapeutic benefits, NSVs may pose safety concerns related to their physicochemical properties, composition, and interaction with biological systems. Assessment of potential toxicity is essential for identifying safety risks and implementing measures to minimize adverse effects associated with NSV-based drug delivery systems[64].

1. Acute Toxicity Studies: Acute toxicity studies evaluate the immediate adverse effects of NSVs following single or short-term exposure in animal models[45]. These studies assess mortality, clinical signs, and gross pathology to determine the maximum tolerated dose and identify potential target organs or tissues affected by NSVs. Acute toxicity data are essential for establishing safe dosing regimens and informing subsequent toxicity assessments[65].

2. Subchronic and Chronic Toxicity Studies: Subchronic and chronic toxicity studies assess the long-term effects of repeated NSV exposure over extended periods, typically ranging from weeks to months[54]. These studies evaluate systemic toxicity, organ toxicity, carcinogenicity, and reproductive toxicity to assess the safety profile of NSVs for prolonged therapeutic use. Histopathological examination of tissues, clinical chemistry analysis, and functional assessments provide comprehensive insights into the potential adverse effects of NSVs over time[33].

3. Genotoxicity and Mutagenicity: Genotoxicity and mutagenicity studies evaluate the potential of NSVs to induce DNA damage or mutations in vitro and in vivo[4]. These studies assess chromosomal aberrations, micronucleus formation, and gene mutations following NSV exposure to identify potential genotoxic hazards and carcinogenic risks associated with NSVs[66].

4. Immunotoxicity: Immunotoxicity assessment evaluates the effects of NSVs on the immune system, including innate and adaptive immune responses, cytokine production, and immune cell activation. These studies assess the immunogenicity, hypersensitivity reactions, and autoimmune responses induced by NSVs to ensure their compatibility with the immune system and minimize inflammatory or allergic reactions[67].

C. Strategies to Mitigate Toxicity Risks:

Mitigating toxicity risks associated with NSVs involves implementing various strategies to enhance their safety profile and minimize adverse effects on biological systems. Some strategies to mitigate toxicity risks include:

1. Surface Modification: Surface modification of NSVs with biocompatible polymers, such as polyethylene glycol (PEG), can improve their stability, reduce protein adsorption, and minimize recognition by the immune system, thereby reducing the risk of immunogenicity and inflammatory responses.

2. Optimization of Formulation Parameters: Optimization of formulation parameters, such as surfactant composition, lipid-to-drug ratio, and vesicle size, can enhance the biocompatibility and safety of NSVs. By carefully selecting formulation components and optimizing preparation methods, researchers can minimize toxicity risks and improve the performance of NSV-based drug delivery systems[68].

3. Encapsulation of Cytoprotective Agents: Encapsulation of cytoprotective agents, such as antioxidants or anti-inflammatory agents, within NSVs can mitigate oxidative stress, inflammation, and tissue damage induced by NSVs, thereby enhancing their safety profile and reducing potential toxicity risks[21].

4. Preclinical Safety Assessment: Comprehensive preclinical safety assessment, including in vitro and in vivo studies, is essential for identifying potential toxicity risks associated with NSVs and informing clinical development. Close collaboration with regulatory authorities and adherence to regulatory guidelines ensure rigorous

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evaluation of NSV safety and facilitate translation to clinical trials[69].

Conclusion

Nano-scale non-ionic surfactant vesicles (NSVs) represent a promising class of drug delivery systems with diverse applications in medicine. Through in vivo studies and clinical trials, NSVs have demonstrated efficacy in targeted drug delivery, controlled release, and overcoming biological barriers for drug delivery. These studies have provided compelling evidence of the therapeutic potential of NSVs in treating various diseases, including cancer, infectious diseases, inflammatory disorders, and neurological conditions. Despite challenges in clinical translation, such as ensuring safety, optimizing pharmacokinetics, and obtaining regulatory approval, ongoing research efforts continue to advance NSV-based drug delivery technologies and overcome these barriers. With further refinement of formulation strategies, manufacturing processes, and regulatory pathways, NSVs hold great promise for revolutionizing drug delivery and improving patient outcomes in the future. Collaborative efforts between researchers, clinicians, industry partners, and regulatory agencies are essential for realizing the full potential of NSVs as safe, effective, and clinically viable drug delivery systems for addressing unmet medical needs and enhancing healthcare delivery worldwide.

Conflict of Interest

None

References

[1] Van Hal, D.A., Bouwstra, J.A., Van Rensen, A., Jeremiasse, E., Vringer, T.D., & Junginger, H.E. (1996). Preparation and characterization of non-ionic surfactant vesicles. Journal of Colloid and Interface Science, 178, 263-273.

[2] Cevc, G., Blume, G., Schatzlein, A., Gebauer, D., & Paul, A. (1996). The skin: a pathway for systemic treatment with patches and lipid-based agent carriers. Advanced Drug Delivery Reviews, 18, 349-378.

[3] Cevc, G. (1996). Transfersomes, liposomes and other lipid suspensions on the skin: permeation enhancement, vesicle penetration, and transdermal drug delivery. Critical Reviews in Therapeutic Drug Carrier Systems, 13, 257-388.

[4] Rangasamy, M., Ayyasamy, B., Raju, S., Gummadevelly, S., & Shaik, S. (2008). Formulation and in vitro evaluation of niosome encapsulated acyclovir. Journal of Pharmaceutical Research, 1, 163-166.

[5] Bhaskaran, S., & Lakshmi, P.K. (2009). Comparative evaluation of niosome formulations prepared by different techniques. Acta Pharmaceutica Scientia, 51, 27-32.

[6] Wadhe, K., Kalsait, R., & Umekar, M. (2009). Alternate drug delivery system: recent advancement and future challenges. Archives of Pharmaceutical Science Research, 1, 97-105.

[7] Bajaj, A., & Desai, M. (2006). Challenges and strategies in novel drug delivery technologies. Pharmaceutical Times, 38, 12-16.

[8] Sankar, V., Ruckmani, K., Durga, S., & Jailani, S. (2010). Proniosomes as drug carriers. Pakistan Journal of Pharmaceutical Sciences, 23, 103-107.

[9] Cable, C. (1989). An examination of the effects of surface modifications on the physicochemical and biological properties of non-ionic surfactant vesicles [Doctoral dissertation, University of Strathclyde].

[10] Attia, I.A., El-Gizawy, S.A., Fouda, M.A., & Donia, A.M. (2007). Influence of a niosomal formulation on the oral bioavailability of acyclovir in rabbits. AAPS PharmSciTech, 8, E106.

[11] D. G. Hall, "Thermodynamics of micelle formation," in Nonionic surfactants: physical chemistry, M. J. Schick, Ed. New York: Marcel Dekker, 1987, vol. 23, pp. 233-296.

[12] S. Zhang and M. E. Morris, "Efflux transporters in drug excretion," in Drug delivery: principles and applications, B. Wang, T. Siahaan, and R. Soltero, Eds. New Jersey: John Wiley & Sons, 2005, pp. 381-398.

[13] A. Shtil, T. M. Grinchuk, and L. Tee, "Overexpression of P-glycoprotein is associated with a decreased mitochondrial transmembrane potential in doxorubixin selected K562 human

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2626-2639 | ISSN:2251-6727

leukemia cells," Int. J. Oncol., vol. 17, pp. 387-392, 2000.

[14] K. Ueda, N. Okamura, and M. Hirai, "Human P-glycoprotein transports cortisol, aldosterone, and dexamethasone, but not progesterone," J. Biol. Chem., vol. 267, pp. 24248-24252, 1992.

[15] M. D. Perloff, L. L. Von Moltke, J. E. Marchand, and D. J. Greenblatt, "Ritonavir induces P-glycoprotein expression, multidrug resistance-associated protein (MRP1) expression, and drug transporter mediated activity in a human intestinal cell line," J. Pharm. Sci., vol. 90, pp. 1829-1837, 2001.

[16] M. T. Huisman, J. W. Smit, H. R. Wiltshire, J. H. Beijnen, and A. H. Schinkel, "Assessing safety and efficacy of directed P-glycoprotein inhibition to improve the pharmacokinetic properties of saquinavir coadministered with ritonavir," J. Pharmacol. Exp. Ther., vol. 304, pp. 596-602, 2003.

[17] S. Duvvuri, M. D. Gandhi, and A. K. Mitra, "Effect of P-glycoprotein on the ocular disposition of a model substrate, quinidine," Curr. Eye Res., vol. 27, pp. 345-353, 2003.

[18] K. Kawazu et al., "Transport of acebutolol through rabbit corneal epithelium," Biol. Pharm. Bull., vol. 29, pp. 846-849, 2006.

[19] P. Arunothayanun et al., "The effect of processing variables on the physical characteristics of non-ionic surfactant vesicles (niosomes) formed from a hexadecyl diglycerol ether," Int. J. Pharm., vol. 201, pp. 7-14, 2000.

[20] M. J. Lawrence et al., "The formation, characterization and stability of non-ionic surfactant vesicles," STP Pharm. Sci., vol. 1, pp. 49-60, 1996.

[21] S. Biswal et al., "Vesicles of non-ionic surfactants (niosomes) and drug delivery potential," Int. J. Pharm. Sci. Nanotechnol., vol. 1, pp. 1-8, 2008.

[22] Shahiwala and A. Misra, "Studies in topical application of niosomally entrapped nimesulide," J. Pharm. Pharm. Sci., vol. 5, pp. 220-225, 2002.

[23] Lavergne et al., "Synthesis and foaming properties of new anionic surfactants based on a renewable building block: sodium dodecyl isosorbide sulfates," J. Colloid Interface Sci., vol. 360, pp. 645-653, 2011.

[24] R. Raymond, J. S. Paul, and C. O. Sian, "Polyoxyethylene alkyl ethers," in Handbook of pharmaceutical excipients, 5th ed. London: Pharmaceutical Press, 2006, pp. 564–571.

[25] Manosroi et al., "Characterization of vesicles prepared with various non-ionic surfactants mixed with cholesterol," Colloid Surf B Biointerfaces, vol. 30, pp. 129-138, 2003.

[26] M. Manconi et al., "Niosomes as carriers for tretinoin II. Influence of vesicular incorporation on tretinoin photostability," Int. J. Pharm., vol. 260, pp. 261-272, 2003.

[27] M. Manconi et al., "Niosomes as carriers for tretinoin. I. Preparation and properties," Int. J. Pharm., vol. 234, pp. 237-248, 2002.

[28] F. Johansson et al., "Brij 58, a polyoxyethylene acyl ether, creates membrane vesicles of uniform sidedness—a new tool to obtain inside-out (cytoplasmic side-out) plasma membrane vesicles," Plant J., vol. 7, pp. 165-173, 1995.

[29] S. Daneshamouz et al., "Influence of liposomes and niosomes on the in vitro permeation and skin retention of finasteride," Ira J. Pharm. Sci., vol. 1, pp. 119-130, 2005.

[30] Pardakhti, M. H. Moshefi, and H. Moteshafi, "Preparation of niosomes containing chloramphenicol sodium succinate and evaluation of their physicochemical and antimicrobial properties," Pharm. Sci. Spr., vol. 1, pp. 11-21, 2007.

[31] Y. Hao, F. Zhao, N. Li, Y. Yang, and K. Li, "Studies on a high encapsulation of colchicine by a niosome system," Int. J. Pharm., vol. 244, pp. 73-80, 2002.

[32] U. Nimmannit and N. Chuansanit, "Factors affecting on entrapment efficiency of retinyl palmitate in nonionic surfactant vesicles," AAPS Pharm. Sci., pp. 993-996, 2003.

[33] S. Guinedi, N. D. Mortada, S. Mansour, and R. M. Hathout, "Preparation and evaluation of reverse-phase evaporation and multilamellar niosomes as ophthalmic carriers of acetazolamide," Int. J. Pharm., vol. 306, pp. 71-82, 2005.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2626-2639 | ISSN:2251-6727

[34] K. Ruckmani, V. Sankar, and M. Sivakumar, "Tissue distribution, pharmacokinetics and stability studies of zidovudine delivered by niosomes and proniosomes," J. Biomed. Nanotechnol., vol. 6, pp. 43-51, 2010.

[35] Z. S. Bayindir and N. Yuksel, "Characterization of niosomes prepared with various nonionic surfactants for paclitaxel oral delivery," J. Pharm. Sci., vol. 99, pp. 2049-2060, 2010.

[36] R. Arora and A. Sharma, "Release studies of ketoconazole niosome formulation," J. Global Pharm. Technol., vol. 2, pp. 125-127, 2010.

[37] K. Srikanth, M. Nappinnai, V. R. M. Gupta, and J. Suribabu, "Niosomes: a prominent tool for transdermal drug delivery," Res. J. Pharm. Bio Chem. Sci., vol. 1, pp. 308-316, 2010.

[38] M. J. Martin, "Pharmaceutical manufacturing of liposomes," in Specialized drug delivery systems manufacturing and production technology, P. Tyle, Ed. New York: Marcel Dekker, 1990, pp. 267–314.

[39] L. D. Mayer, M. B. Bally, M. J. Hope, and P. R. Cultis, "Transmembrane pH gradient drug uptake process," Biochem. Biophys. Acta, vol. 816, pp. 294-302, 1985.

[40] J. Baillie et al., "The preparation and properties of niosomes non-ionic surfactant vesicles," J. Pharm. Pharmacol., vol. 37, pp. 863-868, 1985.

[41] M. N. Azmin et al., "The effect of nonionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice," J. Pharm. Pharmacol., vol. 37, pp. 237-242, 1985.

[42] R. Arora and A. Sharma, "Release studies of ketoprofen niosome formulation," J. Chem. Pharm. Res., vol. 2, pp. 79-82, 2010.

[43] A. H. Sathali and G. Rajalakshmi, "Evaluation of transdermal targeted niosomal drug delivery of terbinafine hydrochloride," Int. J. Pharm. Technol. Res., vol. 2, pp. 2081-2089, 2010.

[44] N. Ahuja et al., "Formulation and evaluation of lansoprazole niosome," Rasayan J. Chem., vol. 1, pp. 561-563, 2008.

[45] S. Gyanendra et al., "Niosomal delivery of isoniazid-development and characterization," Trop. J. Pharm. Res., vol. 10, pp. 203-210, 2011.

[46] K. M. Karim et al., "Niosome: a future of targeted drug delivery systems," J. Adv. Pharm. Technol. Res., vol. 1, pp. 374-380, 2010.

[47] L. S. Frank and L. Huang, "Large scale production of DC-Chol cationic liposomes by microfluidization," Int. J. Pharm., vol. 144, pp. 131-139, 1996.

[48] S. Ahamed, P. Bhatt, S. J. Sultanuddin, R. Walia, M. A. Haque, and S. B. InayathAhamed, "An Intelligent IoT enabled Health Care Surveillance using Machine Learning," in 2022 International Conference on Advances in Computing, Communication and Applied Informatics (ACCAI), IEEE, 2022.

[49] V. Ahmed, S. Sharma, and P. Bhatt, "Formulation and evaluation of sustained release tablet of diltiazem hydrochloride," Int. J. Pharm. Sci. Res., vol. 11, no. 5, pp. 2193-2198, 2020.

[50] A. E. Al-Snafi, S. Singh, P. Bhatt, and V. Kumar, "A review on prescription and non-prescription appetite suppressants and evidence-based method to treat overweight and obesity," GSC biol pharm sci, vol. 19, no. 3, pp. 148–155, 2022.

[51] P. Bhatt et al., "Functional and tableting properties of alkali-isolated and phosphorylated barnyard millet (Echinochloa esculenta) starch," ACS Omega, vol. 8, no. 33, pp. 30294–305, 2023.

[52] P. Bhatt, "Mouth Dissolving Tablets Challenges, Preparation Strategies with a Special Emphasis on Losartan Potassium–A Review," World J. Pharm. Pharm. Sci., vol. 7, no. 9, pp. 271-287, 2018.

[53] C. Goyal, P. Bhatt, S. Rawat, V. Kumar Sharma, and M. Rani Ahuja, "Estimation of shelf-life of Balachaturbhadrika syrup containing different sweetening agents," Res J Pharm Technol, pp. 5078–5083, 2022.

[54] A. Kumar, P. Bhatt, and N. Mishra, "Irritable bowel Syndrome with reference of Alosetron Hydrochloride and Excipient profile used in the manufacturing of Alosetron tablet-A review," J Chem Pharm Sci, vol. 12, no. 03, pp. 71–78, 2019.

[55] M. K. Malik, P. Bhatt, and T. Kumar, "Significance of chemically derivatized starch as drug carrier in

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 2626-2639 | ISSN:2251-6727

developing novel drug delivery devices," Nat Prod J, vol. 12, 2022.

[56] M. K. Malik, V. Kumar, J. Singh, P. Bhatt, R. D. Kaushik, G. Sharma, and S. Kumar, "Preclinical safety assessment of chemically cross-linked modified mandua starch: Acute and sub-acute oral toxicity studies in Swiss albino mice," ACS Omega, vol. 7, no. 40, pp. 35506–35514, 2022.

[57] M. K. Malik, V. Kumar, J. Singh, P. Bhatt, R. Dixit, and S. Kumar, "Phosphorylation of alkali extracted mandua starch by STPP/STMP for improving digestion resistibility," ACS Omega, vol. 8, no. 13, pp. 11750–11767, 2023.

[58] S. Singh, H. Rastogi, V. Deva, R. Dixit, T. Gupta, and M. Tyagi, "Alginate based Nanoparticles and Its Application in Drug Delivery Systems," J. Pharm. Negative Results, pp. 1463-1469, 2022.

[59] Bhatt, P., Kumar, V., Subramaniyan, V., Nagarajan, K., Sekar, M., Chinni, S. V., et al. (2023). Plasma modification techniques for natural polymer-based drug delivery systems. Pharmaceutics, 15(8), 2066.

[60] Varshosaz J., Pardakhty ABaharanchi S.M. Sorbitan monopalmitate-based proniosomes for transdermal delivery of chlorpheniramine maleate. Drug Deliv. 2005;12:75–82. doi: 10.1080/10717540490446044.

[61] Mavaddati M.A., Moztarzadeh F., Baghbani F. Effect of Formulation and Processing Variables on Dexamethasone Entrapment and Release of Niosomes. J. Clust. Sci. 2015;26:1–14. doi: 10.1007/s10876-015-0908-4.

[62] Balakrishnan P., Shanmugam S., Lee W.S., Lee W.M., Kim J.O., Oh D.H., Kim D.D., Kim J.S., Yoo B.K., Choi H.G., et al. Formulation and in vitro assessment of minoxidil niosomes for enhanced skin delivery. Int. J. Pharm. 2009;377:1–8. doi: 10.1016/j.ijpharm.2009.04.020.

[63] Agarwal R., Katare O.P., Vyas S.P. Preparation and in vitro evaluation of liposomal/niosomal delivery systems for antipsoriatic drug dithranol. Int. J. Pharm. 2001;228:43–52. doi: 10.1016/S0378-5173(01)00810-9.

[64] Guinedi A.S., Mortada N.D., Mansour S., Hathout R.M. Preparation and evaluation of reverse-phase evaporation and multilamellar niosomes as ophthalmic carriers of acetazolamide. Int. J. Pharm. 2005;306:71–82. doi: 10.1016/j.ijpharm.2005.09.023.

[65] Mehta S.K., Jindal N., Kaur G. Quantitative investigation, stability and in vitro release studies of anti-TB drugs in Triton niosomes. Colloids Surf. B Biointerfaces. 2011;87:173–179. doi: 10.1016/j.colsurfb.2011.05.018.

[66] Anna M., Katharina L. Polymer micro- and nanocapsules as biological carriers with multifunctional properties. Macromol. Biosci. 2014;14:458–477.

[67] Rinaldi F., Hanieh P.N., Chan L.K.N. Chitosan Glutamate-Coated Niosomes A Proposal for Nose-to-Brain Delivery. Pharmaceutics. 2018;10:38. doi: 10.3390/pharmaceutics10020038.

[68] Tangri P., Khurana S. Niosomes: Formulation and evaluation. Int. J. Biopharm. 2011;2:47–53.

[69] Shi B., Fang C., Pei Y. Stealth PEG-PHDCA niosomes: effects of chain length of PEG and particle size on niosomes surface properties, in vitro drug release, phagocytic uptake, in vivo pharmacokinetics and antitumor activity. J. Pharm. Sci. 2006;95:1873–1887. doi: 10.1002/jps.20491.